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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,502	03/30/2004	Nicholas C. Nicolaides	MOR-0277	5311
23377 7590 10/29/2008 WOODCOCK WASHBURN LLP CIRA CENTRE, 12TH FLOOR 2929 ARCH STREET PHILADELPHIA, PA 19104-2891				
EXAMINER				
POPA, ILEANA				
ART UNIT		PAPER NUMBER		
1633				
MAIL DATE		DELIVERY MODE		
10/29/2008		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/813,502

Applicant(s)

NICOLAIDES ET AL.

Examiner

ILEANA POPA

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 May 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 70, 72, 74-76 and 78 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 70, 72, 74-76, and 78 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SI/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. Claims 1-69, 71, 73, and 77 have been cancelled. Claims 70, 72, and 76 have been amended. Claim 78 is new.

Claims 70, 72, 74-76, and 78 are pending and under examination.

2. All rejections/objections pertaining to claims 73 and 77 are moot because Applicant cancelled the claims in the reply filed on 05/09/2008.

Response to Arguments

Claim Objections

3. The objection to claim 70 is withdrawn in response to Applicant's amendment to the claim filed on 05/09/2008.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d

438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 70, 72, 74-76 remain and the new claim 78 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 6 of U.S. Patent No. 6,825,038, in view of Parkhurst et al. (J Immunol, 1996, 157: 2539-2548). Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

It is noted that the obviousness-type double patenting rejections over the 6,825,038 patent claims was previously withdrawn in response to the submission of a terminal disclaimer on 10/01/2007 (see the non-final Office action mailed on 01/02/2008). However, since the 6,825,038 patent and the present application are not commonly owned and the terminal disclaimer is erroneous (see Applicant's comments in the reply filed on 05/09/2008), the rejection is hereby reinstated as follows:

The instant claims are drawn to a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into the cell expressing a preselected immunogen *in vitro* a nucleic acid encoding the first 133 amino acids of PMS2 (i.e., a dominant negative allele of a PMS2 gene), selecting the cells comprising a mutation in the preselected immunogen that results in enhanced antigenicity, and

expressing the polynucleotide sequence encoding the preselected immunogen in a second genetically stable cell; the method further comprises culturing the second cell (claims 70 and 78). The nucleic acid encoding the first 133 amino acids of PMS2 comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), and selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76). Introduction of the polynucleotide comprising the dominant negative PMS2 into the cell expressing the preselected immunogen can take place in the presence of a DNA mutagen (claim 72). Although the application claims do not recite controlling hPMS2-134 expression by an inducible promoter, one of skill in the art would have been motivated to modify the claimed invention and use such because inactivating hPMS2-134 would be easily achieved when needed, without additional manipulations.

The patent claims recite an *in vitro* method for generating a mutation in a gene of interest in a hypermutable cell (i.e., generating a hypermutated immunogen) by introducing into the hypermutable cell expressing the gene of interest a dominant negative PMS2 allele under the control of an inducible promoter, testing the cell for a mutation in the gene of interest, and stabilizing the genome of the cell expressing the mutated gene of interest by decreasing the activity of the dominant negative allele (claims 1 and 6), i.e., selecting cells comprising a mutation in the gene of interest. Testing comprises analyzing the nucleotide sequence of the gene of interest (claim 2) or the mRNA transcribed from the gene of interest (claim 3). With respect to the limitation

of comparing these sequences to the wild type, this is a requirement for the testing method. The specification discloses that DNA mutagens can be used to enhance the mutation rate (column 2, lines 61-65, column 9, lines 45-49) and that the dominant negative PMS2 allele comprises a truncation mutation at codon 134 resulting in a shorter polypeptide comprising the first 133 amino acids of PMS2 (column 6, lines 30-44), i.e., it is the same as the instant truncated mutant and therefore, the truncation mutations is a thymidine at position 424 of the wild type hPMS2. The patent claims do not recite expressing the mutated and enhanced immunogen into a second, genetically stable cell. However, doing such would have been obvious to one of skill in the art. Upon identification of the desired mutations in the pre-selected immunogen, one of skill in the art would have been motivated to express the immunogen in a genetically stable cell in order to obtain continuous expression of the identified immunogen. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the identifying/selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity.

Since the claims of the U. S. Patent No. 6,825,038 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

6. Claims 70, 72, 74-76 remain and the new claim 78 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-13 and 16-18 of U.S. Patent No. 6,146,894, in view of Parkhurst et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because are obvious variants.

The instant claims are drawn to a method of making a genetically stable cell that produces a hypermutated immunogen by introducing into the cell expressing a preselected immunogen *in vitro* a nucleic acid encoding the first 133 amino acids of PMS2 (i.e., a dominant negative allele of a PMS2 gene), selecting the cells comprising a mutation in the preselected immunogen that results in enhanced antigenicity (i.e., obtaining a homogeneous composition of cultured hypermutable, cells comprising a dominant negative allele of PMS2), and expressing the polynucleotide sequence encoding the preselected immunogen in a second genetically stable cell; the method further comprises culturing the second cell (claims 70 and 78). The nucleic acid encoding the first 133 amino acids of PMS2 comprises a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 (claim 75), and selecting is by determining that the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild

type (claim 76). Introduction of the polynucleotide comprising the dominant negative PMS2 into the cell expressing the preselected immunogen can take place in the presence of a DNA mutagen (claim 72).

The patent claims are drawn to: **(i)** a method of generating a mutation in a gene of interest (i.e., a preselected immunogen) by growing a population of mammalian cells expressing the gene of interest and a dominant negative allele of a PMS2 gene, wherein the dominant negative allele is a truncated human PMS2 (i.e., *in vitro* introduction, into the cell expressing a preselected immunogen, of a dominant negative allele of a PMS2 gene) and identifying a cell in which the preselected immunogen is mutated (i.e., selecting the cell), wherein the cell is hypermutable (i.e., a method of generating a hypermutated preselected immunogen) (claims 11 and 16-18). Identifying/selection is by analyzing the sequence of the gene of interest or of the mRNA transcribed from the gene of interest (claims 12 and 13), i.e., determining whether the polynucleotide comprises a mutation as compared to the wild type, and **(ii)** a homogenous composition of cultured hypermutable, mammalian cells comprising a dominant negative allele of PMS2 (claim 7), wherein the dominant negative allele of PMS2 is human PMS2 (claim 8) comprising the first 133 amino acids of the human PMS2 (claims 9 and 10). The specification also defines that the dominant negative used in the method comprises a truncation mutation at codon 134 resulting in a shorter polypeptide comprising the first 133 amino acids of PMS2 (column 4, lines 8-18), i.e., it is the same as the instant truncated mutant and therefore, the truncation mutations is a thymidine at position 424 of the wild type hPMS2. With respect to the limitation of selecting for cells comprising a

mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches that mutations in wild type antigens could result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the identifying/selecting step would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. The patent claims do not recite expressing the mutated and enhanced immunogen into a second, genetically stable cell. However, doing such would have been obvious to one of skill in the art. Upon identification of the desired mutations in the pre-selected immunogen, one of skill in the art would have been motivated to express the immunogen in a genetically stable cell in order to obtain continuous expression of the identified immunogen.

Since the claims of the U. S. Patent No. 6,146,894 embrace all the limitations of the instant claims, the patent claims and the application claims are obvious variants of each another.

Applicant traversed both obviousness-type double patenting rejections on the grounds that the Examiner was incorrect in asserting that Parkhurst teaches a selection step that would necessarily render cells expressing a preselected immunogen with enhanced antigenicity (Office Action, page 6). Applicant argues that Parkhurst hypothesizes a relationship between immunogenicity and MHC-binding affinity for viral antigens (p. 2538). Applicant submits that Parkhurst discloses that, based on known

relationships between peptide modifications and binding affinity, selected mutations were introduced into viral antigens (p. 2540), that modified viral antigens having increased binding affinity were selected as candidates for further evaluation of immunogenicity, and that in some cases, the selected candidates were demonstrated not to yield enhanced immunogenicity. (p. 2542). Applicant argues that, since Parkhurst teaches that select mutations in MHC-binding anchor positions of viral antigens may or may not also correlate to increased immunogenicity, one of skill in the art would not have predicted that inhibition of mismatch repair as taught by the claims of U.S. Patent Nos. 6,825,038 and 6,146,894, which generates genome-wide mutations, could effect mutations in antigens to increase antigenicity or immunogenicity. Therefore, Applicant requests the withdrawal of the rejections.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant argues that the Examiner was incorrect in asserting that Parkhurst teaches a selection step that would necessarily render cells expressing a pre-selected immunogen with enhanced antigenicity (Office Action, page 6). With respect to this argument, it is noted that the Examiner never asserted such. Parkhurst was cited as evidence that introducing mutations in wild type antigens could result in mutants exhibiting increased immunogenicity. The Examiner stated that, since the art teaches that mutations in wild type antigens could result in increased antigenicity, the identifying/selecting step recited in the claims of the '038 and '894 patents would necessarily render cells expressing a preselected immunogen with enhanced

antigenicity. It is noted that the method recited in the claims of the '038 and '894 patents (i.e., using a dominant negative PMS2 to inhibit mismatch repair) would only generate random genome-wide mutations (including random mutations in the pre-selected immunogen), wherein such mutations would result in an immunogen with unmodified, increased, or decreased antigenicity or immunogenicity (it is noted that there is no recitation in the claims, nor is there a teaching in the art that inhibition of mismatch repair only results in mutants with increased antigenicity or immunogenicity). Based on this, one of skill in the art would readily understand that a selection step, as recited in the patent claims would necessarily identify mutants with enhanced antigenicity or immunogenicity. Applicant argues that, since Parkhurst discloses some mutants with increased binding affinity for the class I MHC molecules without exhibiting enhanced immunogenicity, one of skill in the art would not have predicted that inhibition of mismatch repair could effect mutations in antigens to increase antigenicity or immunogenicity. Such is just an argument not supported by any evidence. Just because some mutants with increased affinity for the class I MHC do not have enhanced immunogenicity does not mean that one of skill in the art could not have predicted that the random mutagenesis method recited in the patent claims would yield enhanced immunogens. That not all Parkhurst's mutations result in enhanced immunogenicity is consistent with a random mutagenesis process as the one recited in the patent claims. Parkhurst recognizes that affinity for the MHC I class molecules does not always correlate with immunogenicity and teach specifically selecting for the enhanced immunogens (Abstract, p. 2545, column 2, p. 2546, column 1). Based on

these teachings, one of skill in the art would readily recognize that a random mutagenesis process would result in enhanced antigens or immunogens and that the selecting step recited in the patent claims would identify such antigens or immunogens. One of skill in the art would consider the patent claims and the instant claims obvious variants.

For these reasons, Applicant's arguments are not found persuasive and the rejections are maintained.

Claim Rejections - 35 USC § 112, new matter

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 70, 72, 74-76, remain and the new claim and 78 is rejected under 35

U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the non-final Office action of 01/02/2008.

Applicant's arguments filed 05/09/2008 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that the specification provides support for the recitation of expressing the mutated gene encoding the pre-selected immunogen in a genetically stable cell (p. 3, lines 15-18 and p. 12, lines 15-21). Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged however, the rejection is maintained for the following reasons:

The instant specification only provides support for expressing the mutated gene encoding the pre-selected immunogen in a genetically stable cell, wherein the genetically stable cell is obtained by restoring the genetic stability of the hypermutable cell via suppressing the expression of the dominant negative PMS2 (p. 5, lines 14-23, p. 12, lines 15-21). The instant specification does not provide support for the embodiment of expressing the gene encoding the mutated pre-selected immunogen in a second cell, wherein the second cell is genetically stable, as recited in the instant claims (it is noted that, although not specifically recited in the claims, such an embodiment encompasses isolating the mutated pre-selected immunogen and expressing it in a second, genetically stable cell). On p. 3, lines 15-18, the specification recites generating genetically altered cell lines expressing antigenic or immunogenic polypeptides; this is not the same with isolating the mutated pre-selected immunogen and expressing it in a second cell. On p. 12, lines 15-21, the specification discloses obtaining the genetically stable cell expressing the mutated pre-selected immunogen by restoring the genetic stability of the hypermutable cell via suppressing the expression of the dominant negative PMS2, i.e., the mutated pre-selected immunogen is not isolated and expressed in a second, genetically stable cell. A search of the remaining portions of the specification failed to provide literal support for expressing the mutated pre-selected immunogen in a second, genetically stable cell. For these reasons, it is concluded that

the amendments to the claims to recite expression of the mutated pre-selected immunogen in a second cell introduce new matter and the rejection is maintained.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 70, 72, 74-76, remain and the new claim and 78 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolaides et al. (Mol. Cell. Biol., 1998, 18: 1635-1641), in view of each Nicolaides et al. (U.S. Patent 6,825,038), Parkhurst et al. (J Immunol, 1996, 157: 2539-2548), and Qin et al. (Oncogene, 1999, 18: 4394-4400).

The applied reference (i.e., U.S. Patent 6,825,038), has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and

that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Nicolaides et al. (Mol. Cell. Biol.) teach a truncated human PMS2 mutant that has a truncation mutation at codon 134 (hPMS2-134), wherein hPMS2-134 has a dominant negative activity and confers a dominant negative MMR defect when transfected into cells (claims 70 and 74) (p. 1635, column 1, p. 1640, column 1). It is noted that the hPMS2-134 of Nicolaides et al. is the same as the one recited in the instant claims and therefore, it must comprise thymidine at nucleotide 424 as the truncation mutation (claim 75). Nicolaides et al. (Mol. Cell. Biol.) also teach a method of producing a hypermutated β -galactosidase (i.e., hypermutated preselected immunogen) by introducing the hPMS2-134 into cells comprising a β -galactosidase reporter gene; introduction of hPMS2-134 into cells disturbs their MMR activity with a resulting higher frequency of mutations within the reporter gene, as opposed to the lack of mutations in the absence of PMS2-134 (claims 70 and 76) (p. 1636, column 2 bridging p. 1637, p. 1637, columns 1 and 2, p. 1638, column 1 and Table 1). Nicolaides et al. (Mol. Cell. Biol.) teach cloning the cells comprising the gene encoding the mutated β -galactosidase, i.e., they teach selection for cells expressing the mutated β -galactosidase and a homogenous culture of these cells (claim 70) (p. 1637, column 2, p. 1638, column 1, Fig. 4). With respect to the limitation of selecting for cells comprising a

mutation resulting in enhanced antigenicity of the preselected immunogen (claim 70), it is noted that the method generates random mutations and that a number of mutations would necessarily result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the cloning step of Nicolaides et al. (Mol Cell Biol) would necessarily render cells expressing a preselected immunogen with enhanced antigenicity.

Nicolaides et al. (Mol. Cell. Biol.) and Parkhurst et al. do not teach a method of making a genetically stable cell that produces a hypermutated immunogen (claims 70 and 78); however, they do teach their method as being useful for molecular evolution (see Nicolaides, Mol. Cell. Boil., p. 1640, column 2, paragraph bridging p. 1641 and p. 1641, column 2). In addition, Nicolaides et al. ('038 patent) also teach a method for molecular evolution and expressing a hypermutated immunogen in a genetically stable cell, the method comprising using hypermutable cells comprising hPMS2-134 and the immunogen of interest, identifying the cell expressing the hypermutated immunogen of interest, and resorting the genetic stability of the identified cell by decreasing hPMS2-134 expression (column 1, lines 54, 55, 64, and 65, column 2, lines 14-22, column 5, lines 65-67, and column 6, lines 1-7, claim 1). Based on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Nicolaides et al. (Mol. Cell. Biol.) and Parkhurst et al. by restoring the genetic stability of their selected cell as taught by Nicolaides et al. ('038 patent), with a

reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain continuous expression of immunogens with enhanced immunogenicity. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that the genetic stability of the hypermutated cell can be successfully restored.

Nicolaides et al. (Mol. Cell. Biol.), Parkhurst et al., and Nicolaides et al. ('038 patent) do not teach expressing their hypermutated immunogen in a second, genetically stable cell. However, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Nicolaides et al. (Mol. Cell. Biol.), Parkhurst et al., and Nicolaides et al. ('038 patent) by expressing the hypermutated immunogen in a second genetically stable cell, with a reasonable expectation of success to achieve the predictable result of obtaining continuous expression of immunogens with enhanced immunogenicity. It is noted that by doing so, one of skill in the art would have practiced a method for making a genetically stable cell which produces a hypermutated immunogen, wherein the hypermutated immunogen has enhanced antigenicity.

Nicolaides et al. (Mol. Cell. Biol.), Parkhurst et al., and Nicolaides et al. ('038 patent) do not teach using a second DNA mutagen (claim 72). However, the prior art teaches that a combination between defective PMS2 activity and DNA mutagens results in a higher mutagenesis rate as compared to either defective PMS2 activity or DNA mutagens alone (see for example Qin et al., Abstract, p. 4399, column 2, last paragraph). It would have been obvious to one of skill in the art, at the time the

invention was made, to modify the method of Nicolaides et al. (Mol. Cell. Biol.), Parkhurst et al., and Nicolaides et al. ('038 patent) by additionally using DNA mutagens, with a reasonable expectation of success. The motivation to do so is provided by Qin et al., who teach a higher rate of mutagenesis in the presence of such agents. One of skill in the art would have been expected to have a reasonable expectation of success in using such because the art teaches the successful use of combinations between DNA mutagens and defective PMS2 to introduce mutations into DNA.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

11. Claims 70, 72, 74-76, remain and the new claim and 78 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolaides et al. (U.S. Patent No. 6,146,894, of record), in view of both Parkhurst et al. and Qin et al.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and

reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Nicolaides et al. teach a method of generating mutations in a gene of interest (i.e., a preselected immunogen) by using hypermutable cells expressing the gene of interest and the human PMS2-134, i.e., Nicolaides et al. teach a method for generating a hypermutated preselected immunogen; the method further comprises identification and selection of cells expressing the hypermutated preselected immunogen (claims 70, 73, and 76) (column 3, lines 50-67, column 4, lines 43-61, column 5 bridging column 6, column 6, lines 1-20, claims 1 and 3). Nicolaides et al. teach their human PMS2-134 as comprising a truncation mutation at codon 134 (claim 74), wherein the truncation mutation is a thymidine at nucleotide 424 of the wild type PMS2 gene (claim 75) (column 4, lines 8-16, claims 5 and 6). With respect to the limitation of determining whether the polynucleotide encoding the preselected immunogen comprises a mutation as compared to the wild type (claim 76), this is a requirement of the method, since in the absence of a comparison there would be no identification of any mutation. With respect to the limitation of selecting for cells comprising a mutation resulting in enhanced antigenicity of the preselected immunogen, it is noted that the method of Nicolaides et al. generates random mutations and that a number of mutations would result in increased antigenicity of the preselected immunogen; the prior art teaches mutations in

the wild type antigens that result in increased antigenicity (see for example Parkhurst et al., Abstract, p. 2540, column 1, first full paragraph, p. 2547, column 1, first full paragraph). Therefore, the selecting step of Nicolaides et al. would necessarily render cells expressing a preselected immunogen with enhanced antigenicity.

Nicolaides et al. and Parkhurst et al. do not specifically teach expressing the hypermutated immunogen in a second, genetically stable cell, i.e., they do not teach a method of making a genetically stable cell that produces a hypermutated immunogen (claim 70). However, Nicolaides et al. do teach their method as being useful for molecular evolution (p. 1640, column 2, paragraph bridging p. 1641 and p. 1641, column 2) and Parkhurst et al. teach the usefulness of obtaining mutants with enhanced immunogenicity for therapy purposes (Abstract, p. 2540, column 1, first full paragraph, p. 2547). Based on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Nicolaides et al. and Parkhurst et al. to obtain variants of immunogens of interest, select for variants with increased immunogenicity, and express them in a second genetically stable cell, with a reasonable expectation of success. One of skill in the art would have been motivated to express immunogens in a genetically stable cell in order to obtain continuous expression of immunogens with enhanced immunogenicity. One of skill in the art would have been expected to have a reasonable expectation of success because the art teaches that protein antigens can be successfully expressed in cells with stable genome. Therefore, the combined teachings of Nicolaides et al. and Parkhurst et al.

disclose a method for making a genetically stable cell which produces a hypermutated immunogen.

Nicolaides et al. taken with Parkhurst et al. do not teach using a second DNA mutagen (claim 72). However, the prior art teaches that a combination between DNA mutagens and defective PMS2 activity results in a higher mutagenesis rate as compared to either DNA mutagens or defective PMS2 activity alone (see for example Qin et al., Abstract, p. 4399, column 2, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Nicolaides et al. by additionally using DNA mutagens, with a reasonable expectation of success. The motivation to do so is provided by Qin et al., who teach a higher rate of mutagenesis in the presence of such agents. One of skill in the art would have been expected to have a reasonable expectation of success in using such because the art teaches the successful use of combinations of DNA mutagens and defective PMS2 to introduce mutations into DNA.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed both obviousness-type rejections on the grounds that the Examiner's assertion that Parkhurst teaches a selection step that would necessarily render cells expressing a preselected immunogen with enhanced antigenicity (Office Action, p. 12 and 16) is incorrect. Applicant argues that Parkhurst hypothesizes a relationship between immunogenicity and MHC-binding affinity for viral antigens (p.

2538). Applicant submits that Parkhurst discloses that, based on known relationships between peptide modifications and binding affinity, selected mutations were introduced into viral antigens (p. 2540), that modified viral antigens having increased binding affinity were selected as candidates for further evaluation of immunogenicity, and that in some cases, the selected candidates were demonstrated not to yield enhanced immunogenicity. (p. 2542). Applicant argues that, since Parkhurst teaches that select mutations in MHC-binding anchor positions of viral antigens may or may not also correlate to increased immunogenicity, one of skill in the art would not have predicted that inhibition of mismatch repair, which generates genome-wide mutations, could effect mutations in antigens to increase antigenicity or immunogenicity. Therefore, Applicant requests the withdrawal of the rejections.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

Applicant argues that the Examiner was incorrect in asserting that Parkhurst teaches a selection step that would necessarily render cells expressing a pre-selected immunogen with enhanced antigenicity (Office Action, pages 12 and 16). With respect to this argument, it is noted that the Examiner never asserted such. Parkhurst was cited as evidence that introducing mutations in wild type antigens could result in mutants exhibiting increased immunogenicity. The Examiner stated that, since the art teaches that mutations in wild type antigens could result in increased antigenicity, the identifying/selecting step disclosed by the prior art would necessarily render cells expressing a preselected immunogen with enhanced antigenicity. It is noted that the

method taught by the prior art cited above (i.e., using a dominant negative PMS2 to inhibit mismatch repair) would only generate random genome-wide mutations (including random mutations in the pre-selected immunogen), wherein such mutations would result in an immunogen with unmodified, increased, or decreased antigenicity or immunogenicity (it is noted that there is no recitation in the claims, nor is there a teaching in the art that inhibition of mismatch repair only results in mutants with increased antigenicity or immunogenicity). Based on this, one of skill in the art would readily understand that a selection step, as taught by the prior art, would necessarily identify mutants with enhanced antigenicity or immunogenicity. Applicant argues that, since Parkhurst discloses some mutants with increased binding affinity for the class I MHC molecules without exhibiting enhanced immunogenicity, one of skill in the art would not have predicted that inhibition of mismatch repair could effect mutations in antigens to increase antigenicity or immunogenicity. Such is just an argument not supported by any evidence. Just because some mutants with increased affinity for the class I MHC do not have enhanced immunogenicity does not mean that one of skill in the art could not have predicted that the random mutagenesis method taught by the prior art would yield enhanced immunogens. That not all Parkhurst's mutations result in enhanced immunogenicity is consistent with a random mutagenesis process as the one disclosed by the prior art. Parkhurst recognizes that affinity for the MHC I class molecules does not always correlate with immunogenicity and teach specifically selecting for the enhanced immunogens (Abstract, p. 2545, column 2, p. 2546, column 1). Based on these teachings, one of skill in the art would readily recognize that a

random mutagenesis process would result in enhanced antigens or immunogens and that the selecting step disclosed by the prior art would identify such antigens or immunogens. One of skill in the art would consider the claimed invention *prima facie* obvious.

For these reasons, Applicant's arguments are not found persuasive and the rejections are maintained.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1633

